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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,245	11/15/2001	Jens Holm	4305/1H942-US2	9286

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DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,245	HOLM ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25,26,28,35,37-39,64 and 66-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25,26,28,35,37-39,64 and 66-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the examiner of record for your application has changed. To aid in paper matching, please address all future correspondence to Michael Szperka, Art Unit 1644, Technology Center 1600.

Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 are pending and under examination as they read on recombinant mutant allergens. It is noted that elected species SEQ ID NO. 36 was found to be free of the prior art. The search of the prior art was halted upon finding art that read on other species of the claimed invention.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. The rejection of claims 1-22, 35, 64, and 66-82 under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/719,553, now published US patent Application 2004 0091500 A1, which has a common inventor with the instant application, has been withdrawn upon reconsideration of the claimed invention. Specifically the copending application does not teach the recited spacing in angstroms between the mutated residues in a mutated allergen.

4. The rejection of claims 1-22, 35, 64, and 66-82 under 35 U.S.C. 102(b) as being anticipated by WO 99/47680 (Reference 1 on the IDS submitted 3-7-02) has been withdrawn upon reconsideration of the claimed invention for the reasons discussed above. Note that the disclosures of WO 99/47680 and US 2004 0091500 A1 are identical.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-96 of copending Application No. 10/719,553. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner by the same method of selection, or if not by an obvious variant thereof. Specifically, Claims 36-96 teach a mutant Bet V1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical between the '719 application and the instant application, such as those recited in copending claim 37 and instant claim 22.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 directed to the same invention as that of claims 36-96 of commonly assigned copending Application No. 10/719,553. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-22, 25, 26, 28, 35, 64, and 66-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ipsen et al., (US 2004/0091500 A1, of record, see entire document).

Ipsen et al. teach recombinant mutant allergens, pharmaceutical compositions comprising said allergens and excipients, and methods of their production (see entire document, particularly the abstract and paragraph 68). These mutant allergens are derived from naturally occurring allergens and comprise substitution mutations at conserved surface-exposed positions among homologous, taxonomically related proteins with a non-conservative amino acid replacement such that the specific binding capacity of the mutant allergen is reduced in comparison to the naturally occurring allergen (see particularly paragraphs 49-55). These mutant allergens are to be made from numerous allergens, including allergens from birch pollen, *Dematophagoides* mites, and animals such as dogs, cat and horses (see particularly paragraphs 56 and 57). The recombinant allergens can comprise one or more substitution mutations (paragraphs 58, 60, 65 and 66) and a working example is provided that comprises four mutations (paragraph 159). Positions to be mutated in the birch tree pollen Bet v 1 comprise substitution at positions 10, 25, 28, 32, 45, 47, 55, 77, and 108, many of the same positions recited in instant claim 22 (see paragraph 58). The substitution mutations are taught as being located in a surface exposed patch that is about 400 angstroms, which happens to be the area covered by an antibody upon binding (see particularly paragraphs 76-81 and 94). The mutants of Ipsen et al. comprise an α-carbon backbone tertiary structure that is essentially the same as the naturally occurring allergen (paragraph 48), and compositions comprising more than one mutant allergen are disclosed (paragraphs 70-74). The data obtained from the working examples of Ipsen indicate that T cell epitopes are maintained and demonstrate a correlation between increasing numbers of mutations and reduced IgE reactivity, with the greatest reduction taking place in the mutant comprising four mutations (see particularly paragraphs 112-167, most particularly paragraph 165). Note that Ipsen et al. did not actually make mutants comprising in excess of four mutations.

These teachings differ from the instant claimed invention in that Ipsen et al. do not teach the spacing of their allergen mutations and did not make a Bet v 1 mutant allergen that comprises mutations at all of the residues discussed above. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make a recombinant mutant Bet v 1 allergen comprising all of these mutations. Motivation to do so comes from the disclosure of Ipsen et al. that Bet v 1 mutants are to comprise multiple mutations and the data of Ipsen et al. which indicate that IgE reactivity decreases as the number of mutations are increased. A person of ordinary skill in the art would have a reasonable expectation of success in making such a mutant based on the numerous working examples of mutant Bet v 1 molecules taught by Ipsen et al.

Note that Ipsen et al. do not teach the spacing of the positions to be mutated relative to each other in the three dimensional structure of Bet v 1. The instant specification teaches that primary and secondary mutations of the instant invention are to be selected from a group that comprises the positions disclosed by Ipsen et al. (see particularly lines 10-17 of the instant specification) and further teaches that primary mutations and secondary mutations can occur at the same amino acid position (see particularly lines 5-8 of page 25). As such a mutant Bet v 1 allergen comprising all mutations at all 9 of the positions taught by Ipsen et al. would minimally comprise 4 primary mutations that are at least 15 angstroms apart.

9. Claims 1-22, 25, 26, 28, 35, 64, and 66-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/47680 (Reference 1 on the IDS submitted 3-7-02, see entire document).

The disclosure of WO 99/47680 is identical to that of US 2004/0091500 A1, differing only in pagination and publication date. As such, the indicated claims are rejected for the same reasons as discussed above in conjunction with the disclosure of US 2004/0091500 A1.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

11. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a genus of mutant allergens and compositions comprising said allergens. These mutants can be derived from any allergen and must comprise at least 4 mutated surface-exposed amino acid residues wherein the mutations are spaced at least 15 angstroms apart. To support this genus, applicant has generated mutants of Bet v 1 comprising at least 4 mutations that have been tested for IgE binding activity (Examples 4, 9, and 10), and has indicated where such mutations are to be made in the allergens Der p 1 and Phl p 5 (see examples 5-8). The disclosure does not provide adequate written support of the claimed genus of allergens for the following reasons:

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri., January 5, 2001, see especially page 1106 column 3).

The breadth of the independent claim reads upon mutants of any naturally occurring allergen, both those known and unknown in the art, and only in dependent

claims 21 and 22 is the breadth narrowed to read on only one allergen. It is known in the art that no a priori structural basis can determine if a molecule will or will not be bound by IgE (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39) and as such there is no core structure found in all allergens that is responsible for IgE binding. Therefore, disclosure of specific mutations in one particular allergen that give rise to reduced IgE binding is not applicable to other allergens. The specification does not disclose mutations for all allergens, an impossible task given that the claims read on allergens that naturally occur yet have not been identified by scientists, and adequate written description cannot be given for something that is unknown. As such, a skilled artisan would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus of mutant allergen polypeptides. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

12. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed mutant allergens comprising mutations that are spaced at least 15 angstroms apart wherein said allergen also comprises reduced specific IgE binding capability. The specification provides working examples of such mutant allergens for the birch pollen allergen Bet v 1(Examples 4, 9, and 10), and provides guidance as to where mutations should be made in the allergens Der p 1 and Phl p 5 (see examples 5-8).

The independent claim recites that comparison to homologous proteins are required in selecting the identity of the amino acid residue that is to be substituted at a position chosen for mutagenesis. It is noted that the specification defines substitution as comprising deletions and additions of single amino acids as well as single amino acid

substitutions (lines 19-22 of page 42), but given that the independent claim recites "substitution of one surface-exposed amino acid residue with another residue" the mutant allergens do not comprise additions or deletions since an addition comprises two residues and a deletion does not comprise any residue. The specification does not define a particular algorithm to be used in determining homology, and it is known in the art that parameters such as gap length, substitution matrices, and percent cutoffs influence homology calculations (The Statistics of Sequence Similarity Scores, downloaded from ncbi.nlm.nih.gov/BLAST/tutorial/Altschul-1.html, see entire document). Calculations made with different parameters will identify different sets of homologous proteins, thus changing the possible amino acids available for substitution.

The independent claim also recites that the mutations are required to be 15 angstroms or more apart. As such, the structure of the naturally occurring allergen must be known prior to generating the mutant allergens. The scope of the independent claim reads on all naturally occurring allergens, including those presently unidentified by scientists and physicians. The structures of all allergens are not known, and crystallization of proteins for structure determination is unpredictable and is based upon trial and error (Kundrot C.E., Cell Mol Life Sci 2004, 525-536, see entire document particularly the abstract). Further, the art teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). The claims recite that the mutant allergen comprises a reduced capability to bind IgE, but guidance as to what positions should be mutated in a native allergen commensurate in scope with the limitations of the instant claims appear to only be provided for the naturally occurring allergens Bet v 1, Der p 1, and Phl p 5.

Dependent claims also recite that the claimed mutant allergen comprises secondary mutations in addition to comprising at least 4 primary mutations. However, the specification teaches that primary mutations and secondary mutations can occur at the same position in the sequence of an allergen, and provides examples of Bet v 1 positions that serve as both primary and secondary mutations (see particularly lines 5-8

of page 25 and lines 10-17 of claim 29). Claim 22 recites specific positions in Bet v 1 that can be mutagenized, but it is not clear if any four recited positions can be used together in the claimed invention, or if only some specific subcombination of mutated positions satisfies the spacing limitations recited in the independent claim. As such, a skilled artisan would not be able to make mutant allergens comprising secondary mutations since he cannot distinguish between primary and secondary mutations, and even within the example of Bet v 1 it is not clear which combinations of mutated positions can be generated to yield a mutant allergen that meets the recited structural limitations.

Therefore, based upon the breath of applicant's claimed invention, the unpredictability concerning the identity of all naturally occurring allergens, the generation of crystallographic data concerning said allergens, the correlation between IgE binding and allergen structure, the identification of amino acid residues suitable for substitution based upon homology, and the inability to distinguish primary from secondary mutations, a skilled artisan would be unable to make and use the full breadth of applicant's claimed invention without conducting undue research.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 3, 15, 22, 37-39 and 83-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 15, 37-39 and 83-85 recite mutant allergens comprising secondary mutations, and compositions comprising said allergens. The criteria for the placement of the secondary mutations are the same criteria recited for the placement of the 4 primary mutations that the mutated allergen must comprise since the specification teaches that the same amino acid position can serve as a primary or secondary mutation (see particularly lines 5-8 of page 25). As such, primary and secondary

mutations appear to be indistinguishable. How can a skilled artisan know if a mutant allergen comprises 4 primary mutations and some secondary mutations or if said allergen comprises more than 4 primary mutations? Further, what is the minimum number of mutations present in a recited allergen that comprises secondary mutations? Only 4 (since the primary mutations can serve as secondary mutations) or greater than 4?

Claim 37 and its dependent claims also recite "recombinant mutant allergen variants according to claim 1". Claim 1 recites "recombinant mutant allergens", but does not identify said allergens as variants. As such the term variant lacks antecedent basis in the claims as currently written.

Claim 22 recites N--7 as a position amenable to substitution, but what does the second hyphen mean? Is the mutation at position 7 of Bet v 1 or is it at –7, whatever that may mean? Further, the claim mixes position nomenclature in that some positions, such as V2, are not hyphenated while other including K-129 are hyphenated. Is there significance to the different nomenclatures?

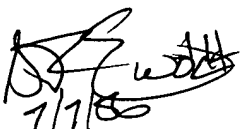
15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
July 3, 2006



G.R. EWOLDT, PH.D.
PRIMARY EXAMINER